PHARMACOPOEIAL DISCUSSION GROUP

CORRECTION

CODE: Q-03/04
NAME: UNIFORMITY OF CONTENT/MASS
(Correction of the sign-off document Rev. 2 signed on 4 November 2015)

Lines 27-33: Addition to the following to the global text: [FOLLOWING

PARAGRAPH NOT ACCEPTED BY THE UNITED STATES PHARMACOPEIA]

Alternatively, products listed in item (4) above that do not meet the 25 mg/25% threshold limit may be tested for uniformity of dosage units by *Mass Variation* instead of the *Content Uniformity* test if the concentration relative standard deviation (RSD) of the drug substance in the final dosage units is not more than 2%, based on process validation data and development data, and if there has been regulatory approval of such a change. The concentration RSD is the RSD of the concentration per dosage unit (w/w or w/v), where concentration per dosage unit equals the assay result per dosage unit divided by the individual dosage unit weight. See the RSD formula in Table 2.
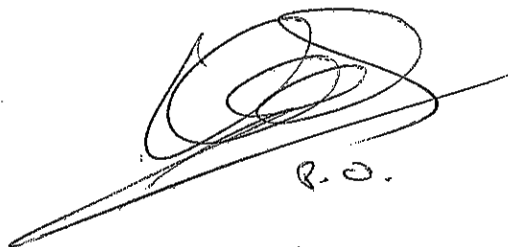
In addition, other editorial corrections were made to ensure consistency with revision 1 signed off on 9 November 2010.

For previous changes related to local and non-harmonized attributes, also see revision 1 signed off 9 November 2010 and the revised cover pages signed off 15 June 2011 and 6 November 2013.

Date: **Signatures:**
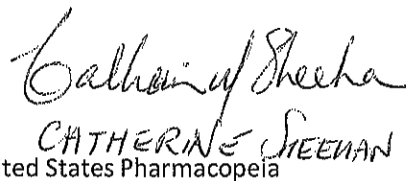
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R.O.   CATHERINE SHEEHAN
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CXS

UNIFORMITY OF DOSAGE UNITS

To ensure the consistency of dosage units, each unit in a batch should have a drug substance content within a narrow range around the label claim. Dosage units are defined as dosage forms containing a single dose or a part of a dose of drug substance in each dosage unit. The uniformity of dosage units specification is not intended to apply to solutions, suspensions, emulsions, or gels in unit-dose containers intended for local action following external, cutaneous administration.

The term "uniformity of dosage unit" is defined as the degree of uniformity in the amount of the drug substance among dosage units. Therefore, the requirements of this chapter apply to each drug substance being comprised in dosage units containing one or more drug substances, unless otherwise specified elsewhere in this Pharmacopeia.

The uniformity of dosage units can be demonstrated by either of two methods, *Content Uniformity* or *Mass Variation* (see *Table 1*). The test for *Content Uniformity* of preparations presented in dosage units is based on the assay of the individual content of drug substance(s) of a number of dosage units to determine whether the individual content is within the limits set. The *Content Uniformity* method may be applied in all cases.

The test for *Mass Variation* is applicable for the following dosage forms:

(1)	Solutions enclosed in unit-dose containers and into soft capsules;
(2)	Solids (including powders, granules, and sterile solids) that are packaged in single-unit containers and contain no active or inactive added substances;
(3)	Solids (including sterile solids) that are packaged in single-unit containers, with or without active or inactive added substances, that have been prepared from true solutions and freeze-dried in the final containers and are labeled to indicate this method of preparation; and
(4)	Hard capsules, uncoated tablets, or film-coated tablets, containing 25 mg or more of a drug substance comprising 25% or more, by weight, of the dosage unit or, in the case of hard capsules, the capsule contents, except that uniformity of other drug substances present in lesser proportions is demonstrated by meeting the requirements for *Content Uniformity*.

The test for *Content Uniformity* is required for all dosage forms not meeting the above conditions for the Mass *Variation* test.

[FOLLOWING PARAGRAPH NOT ACCEPTED BY THE UNITED STATES PHARMACOPEIA]

Alternatively, products listed in item (4) above that do not meet the 25 mg/25% threshold limit may be tested for uniformity of dosage units by *Mass Variation* instead of the *Content Uniformity* test if the concentration relative standard deviation (RSD) of the drug substance in the final dosage units is not more than 2%, based on process validation data and development data, and if there has been regulatory approval of such a change. The concentration RSD is the RSD of the concentration per dosage unit (w/w or w/v), where concentration per dosage unit equals the assay result per dosage unit divided by the individual dosage unit weight. See the RSD formula in Table 2.

Table 1. Application of Content Uniformity (CU) and Mass Variation (MV) Tests for Dosage Forms

Dosage Forms	Type	Subtype	≥25 mg and ≥25%	<25 mg or <25%
Tablets	Uncoated		MV	CU
	Coated	Film	MV	CU
		Others	CU	CU
Capsules	Hard		MV	CU
	Soft	Suspension, emulsion, or gel	CU	CU
		Solutions	MV	MV
Solids in single-unit containers	Single component		MV	MV
	Multiple components	Solution freeze-dried in final container	MV	MV
		Others	CU	CU
Solutions enclosed in unit-dose containers			MV	MV
Others— Dosage forms not addressed by the other categories in this table including but not limited to suppositories, transdermal systems (patches) and semisolid preparations applied cutaneously and intended for systemic distribution of the drug substance			CU	CU

CONTENT UNIFORMITY

Select not less than 30 units, and proceed as follows for the dosage form designated.

Where different procedures are used for assay of the preparation and for the *Content Uniformity* test, it may be necessary to establish a correction factor to be applied to the results of the latter.

Solid Dosage Forms

Assay 10 units individually using an appropriate analytical method. Calculate the acceptance value (see *Table 2*).

Liquid or Semi-Solid Dosage Forms

Assay 10 units individually using an appropriate analytical method. Carry out the assay on the amount of well-mixed material that is removed from an individual container in conditions of normal use, and express the results as delivered dose. Calculate the acceptance value (see *Table 2*).

Calculation of Acceptance Value

Calculate the acceptance value by the formula:

$$\left| M - \bar{X} \right| + ks$$

in which the terms are as defined in *Table 2*.

Table 2

Variable	Definition	Conditions	Value
$\overline{X}$	Mean of individual contents $(\chi_1, \chi_2, \ldots, \chi_n)$, expressed as a percentage of the label claim		
$\chi_1, \chi_2, \ldots, \chi_n$	Individual contents of the dosage units tested, expressed as a percentage of the label claim		
n	Sample size (number of units in a sample)		
k	Acceptability constant	If n = 10, then	2.4
		If n = 30, then	2.0
s	Sample standard deviation		$\left[\dfrac{\sum_{i=1}^{n}(\chi_i - \overline{X})^2}{n-1}\right]^{\frac{1}{2}}$
RSD	Relative standard deviation (the sample standard deviation expressed as a percentage of the mean)		$100s/\overline{X}$
M (case 1) to be applied when T ≤101.5	Reference value	If 98.5% ≤ $\overline{X}$ ≤101.5%, then	$M = \overline{X}$ (AV = ks)
		If $\overline{X}$ <98.5%, then	M = 98.5% (AV = 98.5 − $\overline{X}$ + ks)
		If $\overline{X}$ >101.5%, then	M = 101.5% (AV = $\overline{X}$ − 101.5 + ks)
M (case 2) to be applied when T >101.5	Reference value	If 98.5 ≤ $\overline{X}$ ≤T, then	M = $\overline{X}$ (AV=ks)
		If $\overline{X}$ <98.5%, then	M =98.5% (AV= 98.5 − $\overline{X}$ + ks)
		If $\overline{X}$ >T, then	M = T% (AV= $\overline{X}$ − T + ks)
Acceptance value (AV)			General formula: $\left|M - \overline{X}\right| + ks$ (Calculations are specified above for the different cases.)
L1	Maximum allowed acceptance value		L1 = 15.0 unless otherwise specified
L2	Maximum allowed range for deviation of each dosage unit tested from the calculated value of M	On the low side, no dosage unit result can be less than 0.75M, while on the high side, no dosage unit result can be greater than 1.25M. (This is based on an L2 value of 25.0.)	L2 = 25.0 unless otherwise specified

Variable	Definition	Conditions	Value
T	Target content per dosage unit at the time of manufacture, expressed as a percentage of the label claim. Unless otherwise stated, T is 100.0%, or T is the manufacturer's approved target content per dosage unit.		

MASS VARIATION

Carry out an assay for the drug substance(s) on a representative sample of the batch using an appropriate analytical method. This value is result A, expressed as percentage of label claim (see *Calculation of Acceptance Value*). Assume that the concentration (weight of drug substance per weight of dosage unit) is uniform. Select not less than 30 dosage units, and proceed as follows for the dosage form designated.

Uncoated or Film-Coated Tablets

Accurately weigh 10 tablets individually. Calculate the content, expressed as percentage of label claim, of each tablet from the mass of the individual tablet and the result of the assay. Calculate the acceptance value.

Hard Capsules

Accurately weigh 10 capsules individually, taking care to preserve the identity of each capsule. Remove the contents of each capsule by a suitable means. Accurately weigh the emptied shells individually, and calculate for each capsule the net mass of its contents by subtracting the mass of the shell from the respective gross mass. Calculate the drug substance content of each capsule from the mass of the individual capsule and the result of the assay. Calculate the acceptance value.

Soft Capsules

Accurately weigh 10 intact capsules individually to obtain their gross masses taking care to preserve the identity of each capsule. Then cut open the capsules by means of a suitable clean, dry cutting instrument such as scissors or a sharp open blade, and remove the contents by washing with a suitable solvent. Allow the occluded solvent to evaporate from the shells at room temperature over a period of about 30 minutes, taking precautions to avoid uptake or loss of moisture. Weigh the individual shells, and calculate the net contents. Calculate the drug substance content in each capsule from the mass of product removed from the individual capsules and the result of the assay. Calculate the acceptance value.

Solid Dosage Forms Other Than Tablets and Capsules

Proceed as directed for *Hard Capsules*, treating each dosage unit as described therein. Calculate the acceptance value.

Liquid Dosage Forms

Accurately weigh the amount of liquid that is removed from each of 10 individual containers in

122   conditions of normal use. If necessary, compute the equivalent volume after determining the density.
123   Calculate the drug substance content in each container from the mass of product removed from the
124   individual containers and the result of the assay. Calculate the acceptance value.

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Calculation of Acceptance Value

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128   Calculate the acceptance value as shown in *Content Uniformity*, except that the individual contents of
129   the dosage units are replaced with the individual estimated contents defined below.

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$x_1, x_2, \ldots, x_n$	=	individual estimated contents of the dosage units tested, where $x_i = w_i \times A/\overline{w}$
$w_1, w_2, \ldots, w_n$	=	individual masses of the dosage units tested
A	=	content of drug substance (% of label claim) obtained using an appropriate analytical method
$\overline{w}$	=	mean of individual masses $(w_1, w_2, \ldots, w_n)$

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134   **CRITERIA**
135   Apply the following criteria, unless otherwise specified.

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137   ### Solid, Semi-Solid, and Liquid Dosage Forms

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139   The requirements for dosage uniformity are met if the acceptance value of the first 10 dosage units is less than
140   or equal to L1%. If the acceptance value is greater than L1%, test the next 20 dosage units, and calculate the
141   acceptance value. The requirements are met if the final acceptance value of the 30 dosage units is less than
142   L1%, and no individual content of the dosage unit is less than [1 − (0.01)(L2)]M nor more than [1 +
143   (0.01)(L2)]M in the *Calculation of Acceptance Value* under *Content Uniformity* or under *Mass Variation*. Unless
144   otherwise specified, L1 is 15.0 and L2 is 25.0.